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UPDATE IN CLINICAL NEUROGENETICS

# Ataxia with vitamin E deficiency: update of molecular diagnosis

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**Abstract** Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive neurodegenerative disease, due to mutations in TTPA gene (Arita et al. in Biochem J 306(Pt. 2):437–443, 1995; Hentati et al. in Ann Neurol 39:295–300, 1996), which encodes for α-TTP, a cytosolic liver protein that is presumed to function in the intracellular transport of α-tocopherol. This disease is characterized clinically by symptoms with often striking resemblance to those of Friedreich ataxia. The neurological symptoms include ataxia, dysarthria, hyporeflexia, and decreased vibration sense, sometimes associated with cardiomyopathy and retinitis pigmentosa (Mariotti et al. in Neurol Sci 25:130–137, 2004). Vitamin E supplementation improves symptoms and prevents disease progress (Doria-Lamba et al. in Eur J Pediatr 165(7):494–495, 2006). Over 20 mutations have been identified in patients with AVED. In the present paper we summarize the recent findings on molecular genetic of this disease including the list of the known mutations.

**Keywords** Ataxia · Vitamin E · TTPA gene · Retinitis pigmentosa

## Introduction and clinical symptoms

Ataxia with isolated vitamin E deficiency (AVED; MIM# 277460) is a rare autosomal recessive neurodegenerative disease, due to the defect of α-TTP, an intracellular cytosolic protein that bounds specifically to α-tocopherol [25].

The clinical phenotype resembles Friedreich's ataxia, although Friedreich's ataxia is more often accompanied by cardiomyopathy and impaired glucose metabolism [28]. Several features are shared with Friedreich ataxia, including cerebellar ataxia, loss of deep tendon reflexes, vibratory-sense disturbances, dysarthria, muscle weakness, and Babinski sign [16]. However, cardiomyopathy is significantly rarer in AVED than in Friedreich ataxia, whereas head titubation and dystonia appeared to be specific to AVED [10]. Generally, there is no scoliosis or foot deformity. Magnetic resonance imaging (MRI) of brain and nerve conduction are normal in most of cases (Fogel et al. 2007). The concomitant presence of specific neurological symptoms and very low levels of plasma vitamin E, in the absence of other clinical conditions commonly associated with fat malabsorption, can guide the differential diagnosis [2]. The disease can be diagnosed by clinical features associated with low levels of vitamin E of serum. Genetic diagnosis is possible but not necessary [8].

The phenotype of AVED also resembles abetalipoproteinemia since clinical signs in both diseases are caused by vitamin E deficiency. However, unlike AVED, vitamin E deficiency in abetalipoproteinemia is due to a gastrointestinal lipid uptake syndrome that leads to severe diarrhea. Patients have a very low serum vitamin E level (<3 mg/L; reference values 3–15 mg/L), with a normal intestinal fat absorption mechanism and no signs of abetalipoproteinemia. Since 1981, familial isolated vitamin E deficiency has been described [9], and despite the small number of cases initially reported, phenotypic variability appeared very great, ranging from severe Friedreich-like ataxia presentation (AVED) to mild neurological impairment and very late disease onset [36].

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The treatment is supplementation with vitamin E up to 800 mg/day [29]. The administration of vitamin E supplements has resulted in cessation of the progression of the neurologic symptoms and signs in most patients and in a melioration of established neurologic abnormalities in some of them [18]. In other cases, there has been no improvement. The extent of recovery clearly is related to when the therapy is begun: the more advanced the deficit, the more limited the response to therapy [14]. It suggests that a prompt genetic characterization of AVED may prompt an early effective treatment of the disease. Hence, early diagnosis of vitamin E deficiency may provide considerable improvement in the quality of AVED patient's life [41].

## Molecular genetics

AVED is caused by mutations in the α-tocopherol transport protein (α-TTP) gene, which is located at chromosome 8q13 [33]. The gene consists of five exons.

α-TTP is able to selectively bind α-tocopherol (the most active vitamin E isomer) to the very-low-density lipoproteins (VLDLs) in the liver, which are released in the blood circulation. α-TTP is a cytosolic liver protein that is presumed to function in the intracellular transport of α-tocopherol [52]. The pathogenic basis of such ataxias at this time appears to involve two broad types of processes: free-radical injury and defects of DNA single- or double-strand break repair [24].

Vitamin E is a fat-soluble antioxidant that prevents lipid oxidation in the membranes. There are various forms of vitamin E, such as α-, β-, γ- and δ-tocopherol. α-tocopherol is regarded as the most biologically effective. Vitamin E is absorbed in the small intestine and transported in chylomicrons to the liver. In the liver α-tocopherol is incorporated into nascent VLDLs, which then enter the circulation.

Patients with AVED have a mutation of α-TTP gene and therefore cannot include α-tocopherol in the VLDL [17]. The lipid concentrations in their peripheral blood are normal, but vitamin E levels are very low. Because of this low level, the scavenging function fails and neurodegeneration appears most prominently in cerebellum and peripheral nerves. The connection between these pathological findings and vitamin E is not known in detail, but oxidative stress is likely to play a major role [22].

### *TTPA* gene mutations analysis

Table 1 shows the different mutations described until now.

Using rat α-TTP to screen a liver cDNA library, followed by PCR, Arita et al. [4] cloned full-length human α-TTP. The deduced 278-amino acid protein has a calculated molecular mass of 31.7 kD and shares 94% identity with rat α-TTP [40]. Northern blot analysis of several human tissues detected a 4.5-kb α-TTP transcript in liver only *TTPA* gene in the chromosome 8q13.1–q13.3 region [6].

Today mutations on each exon have been described. The most frequent mutations of the *TTPA* gene is the 744delA in exon 5 and the 513insTT mutation in exon 3. In North-African populations, the most frequent mutation responsible for the disease is the 744delA mutation, while in AVED families of North European origin the 513insTT mutation has been often identified [26]. In Italian patients, these two mutations account for approximately 80% of the *TTPA* mutated alleles. Biochemical characterization of *TTPA* missense mutations has been reported for six missense mutations. These studies indicated that *TTPA* mutations (R59W, E141K, and R221W) associated with a severe early-onset AVED exhibit a clear impairment in both binding and transfer activity of TTPA, while the variants associated with the milder late-onset form of the disease (H101Q, A120T, R192H) show biochemical properties similar to the wild-type protein. For other mutations, the possible implication for AVED has been hypothesized on the basis of the crystal structure of the human TTPA protein [30]. The severity of the disease clearly can be modulated by different, nongenetic factors including the amount of vitamin E in the daily diet and the time of initiation and dosage of vitamin E supplementation, once the biochemical diagnosis has been made [5]. However, the phenotype associated with the semiconservative missense mutations (R192H, A120T, and H101Q) appears to be milder than that seen in the majority of cases [12]. The partial loss of function associated with mutations R192H and H101Q is corroborated by the results of previous studies, which used deuterated forms of α-tocopherol stereoisomers (RRR and SRR) [46]. In the study of the function of the hepatic α-TTP in normal humans, a marked preference for the RRR stereoisomer over the SSR form of α-tocopherol was found. The ability to discriminate between the isomers also was demonstrated in perfused monkey livers in vitro. Patients with R192H or H101Q mutations were still able to preferentially incorporate the natural RRR stereoisomer into VLDL, to a lesser extent than normal subjects, and were labeled "discriminators". These patients contrasted with other patients who had a complete loss of the capacity to preferentially incorporate the natural α-tocopherol stereoisomer into VLDL (labeled "nondiscriminators"). In these patients, the mutations have been characterized, and they are homozygous for severe truncating mutations (530AGrGTAAGT, 744delA, 486delT, and R134X). Interestingly, they all are associated with a severe, early-onset form of the disease [31]. All other truncating mutations and the nonconservative

**Table 1** Mutations in the *TTPA* gene

| | Mutation | Location | Effect | NT position | Clinical phenotype | Reference |
|---|---|---|---|---|---|---|
| 1 | C>T | 5′UTR | Decrease in TTP levels | −1 | Severe | [47] |
| 2 | T>C | Ex1 | Disruption of initiation | 2 | ND | [21] |
| 3 | T>G | Ex1 | Disruption of initiation | 2 | ND | Schuelke, unpublished |
| 4 | C>T | Ex1 | Mis-splicing | 175 | Severe | [10] |
| 5 | A>G | Ex1 | D64G | 191 | Severe | [47] |
| 6 | G>C | Intron1 | Premature termination | IV81-1 | ND | [10] |
| 7 | 219insAT | Ex2 | Frameshift | 219–220 | Severe | [26] |
| 8 | delATGGAGTC | Ex2 | Frameshift | 302–309 | Mild | Schuelke, unpublished |
| 9 | T>G | Ex2 | H101Q | 303 | Mild | [10, 19, 35, 49–51] |
| 10 | A>G | Ex2 | Splice-site mutation | 306 | Mild | [10] |
| 11 | G>A | Ex2 | A120T | 358 | Mild | [10] |
| 12 | G>A | Intron2 | Splice donor | IV82+1 | ND | Schuelke, unpublished |
| 13 | C>T | Ex3 | R134X | 400 | ND | [10, 11] |
| 14 | G>T | Ex3 | Premature termination | 421 | ND | [41] |
| 15 | G>A | Ex3 | E141K | 421 | Severe | [10] |
| 16 | 485delT | Ex3 | Frameshift | 485 | Severe | [20] |
| 17 | 486delT | Ex3 | Frameshift | 486 | Severe | [10, 20, 39] |
| 18 | 513insTT | Ex3 | Frameshift | 513–514 | Severe | [1, 10, 11, 20, 26, 27, 33] |
| 19 | AG530GTAAGT | Ex3 | Frameshift | 530–31 | Severe | [9, 10, 33, 42, 46] |
| 20 | G>A | Ex3 | Splice donor | 552 | Severe | [41, 42, 45] |
| 21 | T>C | Ex4 | L183P | 548 | Severe | [43] |
| 22 | T>C | Ex4 | R192H | 575 | Mild | [10, 20] |
| 23 | C>T | Ex4 | R221 W | 661 | Severe | [10] |
| 24 | G>C | Ex5 | G246R | 736 | Mild | [26] |
| 25 | 744delA | Ex5 | Frameshift | 744 | Severe | [1, 3, 7, 10, 26] |

missense mutations (R59W, E141K, and R221W) also seemed to be associated with the severe form of the disease, suggesting that they also result in complete loss of function, although the patients were not studied for their ability to discriminate between RRR and SRR isomers of α-tocopherol [15, 23]

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